DETAILED ACTION

Status of Application, Amendments, and/or Claims

The amendment filed on 01/22/2008 has been entered. Claims 6-9 are amended. Claims 1-21 are pending. Claims 6-9, 20, and 21 are currently under consideration. All other claims are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Withdrawn Objections and/or Rejections

The rejection of claim 6 under 35 U.S.C. 102(b) as being unpatentable over WO 91/05565 (2 May 1991) is withdrawn in view of the amended claim, i.e., the recitation of a limitation, “wherein said latent protein is a refolded protein".

Objection to the Specification

The disclosure is objected to because it refers to the Atty Docket No., which should replaced by the application Number (see page 76). Appropriate correction is required.

Claim Rejections—35 USC § 112, 1st paragraph

(i). The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(ii). Claims 6-9, 20, and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Amended claim 6 recites a limitation, "wherein aid latent protein is a refolded protein", which introduces new matter. Claims 7-9, 20, and 21 depend from claim 6. Inspection of the specification indicates that there is no support for the limitation in the instant disclosure. Specification at page 69, lines 22-24, as asserted by Applicants, does not provide the support for the limitation.

(iii). Claims 6-9, 20, and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The rejection is maintained for the reasons set forth in the previous office action.

(iv). Response to Applicants' argument

Applicants argue the following:

Applicants respectfully submit that the specification provides adequate written description for the latent TGF-β family member fusion proteins recited in the claims. The specification at pages 77-79 discloses various latent TGF-β fusion protein. For example, at page 77, the specification discloses latent fusion proteins wherein the leader sequence is a collagen binding domain, an FB domain of protein A or a hexa-histidine region. The specification discloses that these fusion proteins display little or no activity in a ROS assay but are activated upon cleavage of the N-terminal non-morphogen peptide to yield an active C-terminal morphogen domain. Figure 7A-J and pages 79-82 describe various such fusion proteins. Applicants submit that this disclosure provides the requisite written description for the latent TGF-β fusion protein recited in the claims. Accordingly, applicants request that the Examiner withdraw this rejection.

Applicants' argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, as stated in the previous office action, claims 6-9, 20, and 21 are drawn to a genus of latent TGF-β family member fusion proteins comprising a cleavable leader sequence lined to a TGF-β family protein c-terminal domain. Thus, the claims encompass a genus of cleavable sequences operably linked to a genus of TGF-β family protein C-terminal domains. The claims do not require that the cleavable leader sequences possess any particular conserved structure nor other disclosed distinguishing feature. The instant disclosure fails to provide sufficient description information, such as definitive structural features of the genus of the recited leader sequences. There is no description of the structural feature that makes a leader sequence inhibits the biological activity associated with a TGF-β family protein C-terminal domain and thus renders a TGF-β family member fusion protein latent.

There is no description regarding how to choose a leader sequence, such as one from another TGF-β family protein, to be used as a leader sequence that inhibits the biologically activity associated with a TGF--β family protein C-terminal domain. Thus, the instant disclosure of a fusion protein comprising a leader sequence, a collagen binding domain, an FB domain of protein A or a hexa-histidine region and OP-1 protein (pages 77-82, Figure 7) is not sufficient to support the broad genus of fusion proteins.

Secondly, the instant disclosure fails to disclose a latent TGF family member fusion protein, wherein the latent protein is a refolded protein. By definition of the specification, a latent protein is an inactive protein (page 79, lines 3-4), whereas a refolded protein is presumably to be active (page 79, line 14; page 68). It is clear from the claims that a TGF-β family protein C-terminal domain becomes active on upon cleavage of the leader sequence. However, it is noted that a fusion protein of H2487 comprising a collagen-binding domain and modified OP-1 was successfully refolded and active in the ROS assay (Figure 7A; the 3rd paragraph of page 77 of the specification). Thus, such a fusion protein is not considered as a latent fusion protein because it is active.

Moreover, the prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to identify the genus of leader sequences encompassed by the instant claims. Hall et al. (WO 96/39430, 12 December 1996) teach a TGF-β fusion protein comprising a TGF-β1 active fragment (presumably comprising the C-terminal domain of TGF-β1) and a lead sequence: purification

tag:proteinase site: ECM binding site: proteinase site: TGF-β (page 4, the 2nd paragraph). The TGF-β fusion protein isolated, purified and renatured exhibits an antiproliferative activity comparable to TGF-β1 controls (naturally occurring TGF-β1) (page 8, the 1st and 2nd paragraphs). Hall et al. (U.S. Patent No. 5,800,811, September 1, 1998) provide the same teaching. Likewise, Nimni et al. (U.S. Patent No. 6,352,972 B1, March 5, 2002; 102(e) date: June 3, 1997) teach a fusion protein comprising a leader sequence and TGF/OP-1 (see, e.g., columns 3-4). However, the prior art does not teach such a leader sequence that inhibits the biological activity associated with a TGF-β family protein C-terminal domain and thus renders a TGF-β family member fusion protein latent .

Accordingly, due to the breadth of the genus of recited leader sequences and lack of the definitive structural features of the genus, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the genus of leader sequences and thus the instantly claimed latent TGF-β family member fusion proteins.

Claim Rejections—35 USC § 112, 2nd paragraph

(i). The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

(ii). Claims 6-9, 20, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is indefinite because it recites “wherein said latent protein is a refolded protein”. Since a latent form of a protein is inactive (page 79, lines 3-4), whereas a correctly refolded protein presumably to be active (page 79, line 14; page 68), the two limitations contradict each other, rendering the claim indefinite.

Claim 7 recites “wherein a tissue-targeting domain is embedded within said cleavable lead sequence”, which contradicts to another limitation “whereby cleavage of the leader sequence will not cleave said tissue-targeting domain from said C-terminal domain”. If a tissue-targeting domain is embedded within a cleavable lead sequence, the tissue-targeting domain would necessarily be cleaved from said C-terminal domain when the leader sequence is cleaved off.

Claims 8, 9, 20, and 21 are rejected as dependent claims from claim 6.

(iii). Response to Applicants’ argument

Applicants argue that claim 7 is not unclear and the two portions of the claim identified by the examiner are not contradictory. Applicants argue that claim 6 from which claim 7 depends, recites that the C-terminal domain becomes active upon cleavage of a part or

all of said lead sequence. Applicants argue that claim 7 recites fusion proteins whereby only that portion of the leader sequence that does not include the tissue targeting domain is cleaved.

Applicants' argument has been fully considered, but is not deemed to be persuasive because claim 7 recites "whereby cleavage of the leader sequence will not cleave said tissue-targeting domain from said C-terminal domain"; it does not recite a limitation, such as "whereby cleavage of a part of the leader sequence will not cleave said tissue-targeting domain from said C-terminal domain".

Comment [R1]:

Claim Objections

Claims 6-9 and 20 are objected to because they recite non-elected subject matter (TGF-β family proteins). Appropriate correction is required.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

/Ruixiang Li/

Primary Examiner, Art Unit 1646

Ruixiang Li, Ph.D.
April 16, 2008